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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/620,221	07/15/2003	Gary A. Koppel	22064-71990	8706

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EXAMINER	
ROYDS, LESLIE A	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/620,221	KOPPEL, GARY A.	
	Examiner	Art Unit	
	Leslie A. Royds	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 Jan 07;23 Jul 07;31 Oct 07;21 Feb 08*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-17* is/are pending in the application.

4a) Of the above claim(s) *1,4,7-10 and 12-17* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2,3,5,6 and 11* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *15 July 2003 & 21 July 2005*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-17 are presented for examination.

Acknowledgement is made of the instant application as a continuation (CON) application of U.S. Patent Application No. 09/640,362, filed August 16, 2000, now U.S. Patent No. 6,610,681, which claims priority under 35 U.S.C. 119(e) to U.S. Provisional Patent Application Nos. 60/149,115, filed August 16, 1999; 60/172,452, filed December 17, 1999; 60/176,570, filed January 18, 2000; and 60/194,534, filed April 4, 2000.

Applicant's amendments to the specification at page 1, following the title of the invention, filed February 20, 2007; July 23, 2007; October 31, 2007; and February 21, 2008 have each been received and entered into the present application.

Applicant's Information Disclosure Statements (IDS) filed July 15, 2003 (six pages) and July 21, 2005 (two pages) have each been received and entered into the present application. As reflected by the attached, completed copies of form PTO-1449 (eight pages total), the Examiner has considered the cited references, with the exception of non-patent literature citation numbers KR-KY, LR-LZ, MR-MS, NQ-NU and PR-PT on the IDS filed July 15, 2003. Applicant refers to the previously submitted copies of these documents in prior U.S. Patent Application No. 09/640,362. However, after a reasonable search by the Examiner, said documents could not be located and, therefore, have not been further considered.

Applicant's response filed January 22, 2007 to the requirement for restriction/election dated September 22, 2006 has been received and entered into the present application. Applicant's additional response filed July 23, 2007 to the supplemental requirement for election dated April 23, 2007 has also been received and entered into the present application. Pursuant to the notice dated October 2, 2007, Applicant's response of July 23, 2007 was held non-compliant. Applicant's response filed October 31, 2007 correcting the deficiencies in the response of July 23, 2007 has been received and entered into the present application. Pursuant to the notice dated January 25, 2008, Applicant's response of October 31,

2008 was also held non-compliant. Applicant's response filed February 21, 2008 correcting the deficiencies in the response of October 31, 2008 has been received and entered into the present application.

Requirement for Restriction/Election

Applicant's election **with traverse** of the invention of Group II (claims 2-6), directed to methods for enhancing cognitive function, and the species of (a) dementia as the single disclosed specie of cognitive disorder, (b) clavulanic acid as the single disclosed specie of clavulanic acid compound, and (c) (2R)-anti-5-{3-[4-(10,11-difluoromethanodibenzosuber-5-yl)-piperazin-1-yl]-2-hydroxypropoxy} quinoline as the single disclosed specie of P-glycoprotein efflux pump inhibitor; in the replies filed January 22, 2007, July 23, 2007, October 31, 2007 and February 21, 2008, is acknowledged by the Examiner. In view of the fact that claim 11 was identified as a linking claim and elected claims 2-6 have been amended to now depend from claim 11, examination of the elected group (claims 2-6) will also include examination of generic claim 11.

Applicant traverses the requirement on the grounds that the each of the inventions delineated by the Examiner "shares a substantial technical feature in common, namely clavulanic acid, or a salt thereof, or an active ester form thereof that is hydrolyzed *in vivo* to clavulanic acid". (p.6, Remarks of January 22, 2007). Applicant alleges the Examiner has failed to given sufficient weight to this feature and further alleges that the inventions are neither independent nor distinct, as asserted by the Examiner. Applicant further traverses the election of a specific cognitive disorder as required by the Examiner because Applicant alleges "that dementia, amnesia and Alzheimer's disease are known to people of ordinary skill in the art to be related by a common manifestation of cognitive symptoms". Applicant further alleges that the DSM-IV recognizes these disorders as falling under a similar classification and asserts that the three conditions are linked by a similar neuroanatomical locus, particularly the hippocampus and cerebral

cortex. Applicant states that the treatment of these conditions is effected via modulation of brain glutamate and the search for each of the three is likely to be coextensive and not burdensome to the Examiner. Still further, Applicant relies upon the publication to Jelic et al. to support the assertion that cognitive deficits associated with dementia, amnesia and Alzheimer's disease are amenable to the same type of pharmacologic therapy, such as piracetam or Aricept.

Applicant's traversal has been carefully considered in its entirety, but fails to be persuasive.

Initially, it is noted that the instant requirement for restriction of the inventions designated as Groups I-V is made under the provisions of 35 U.S.C. 121 and not under lack of unity practice as would be required if the instant case were a National Stage (371) filing. Accordingly, arguments directed to a common "special technical feature" as Applicant references in his remarks at pages 6-7 of the response filed January 22, 2007 are clearly not germane to the instant rationale for holding the inventions of Groups I-V patentably distinct and/or independent from one another. Demonstration of patentable distinction and/or independence under 35 U.S.C. 121 is not based upon a lack of special technical feature, but rather based upon the reasoning provided in MPEP §806.05-806.06, wherein processes (such as those claimed) may be held distinct due to different modes of operation, different functions, or different effects and resultant endpoints and a product may be held to be distinct from a process if the product can be used in a materially different process of using the product. Please see pages 3-5, where such reasoning has been provided to demonstrate the distinction between the groups designated as Inventions I-V.

Though Applicant may be correct in stating that Inventions I-V are related in the sense that each employs a clavulanic acid compound, it remains that, despite this commonality between the inventions, each invention is distinct from the others on the grounds that the inventions are distinct therapeutic methods of treatment with different objectives, endpoints and steps or a distinct product that may be used in various materially different methods of use. In view of these facts, the distinctness of each of the inventions is firmly grounded in the guidance provided in the MPEP at §806.05-806.06 and the restriction

among Groups I-V is maintained for the reasons described at pages 3-5 of the Office Action dated September 22, 2006.

Second, the fact that the species of dementia, amnesia and Alzheimer's disease may be related on the basis that each shares a common manifestation of cognitive symptoms that occur in a similar neuroanatomical locus does not change the fact that each of the species listed are independent and/or distinct because they each clearly differ in etiology, pathophysiological manifestations, treatment protocol (i.e., duration of treatment, dosage amounts of active agent, frequency of treatment, etc.) and patient population. Though Applicant alleges that they share similar etiology and pathophysiological manifestations in that each exhibits cognitive symptoms that occur in a similar anatomical location, this is not a point well taken because the etiology of amnesia, such as, e.g., from a traumatic brain injury, would clearly differ from the etiology of Alzheimer's disease, such as, e.g., the formation of extensive beta-amyloid deposits in the brain, which each would differ from the etiology of dementia, such as, e.g., stroke. Furthermore, the duration of therapy, dosage amounts and frequency of treatment necessary to treat each of the conditions would differ depending on the condition to be treated such that the efficacy seen with short-term use of a compound for temporary amnesia would not necessarily anticipate, suggest or render obvious the use of the same compound for a chronic and much more highly complex condition such as Alzheimer's disease. In other words, a comprehensive search of patent and non-patent literature for dementia and/or amnesia *per se* would not necessarily result in a comprehensive search for Alzheimer's disease, particularly because the known complexities of Alzheimer's disease and the lack of effective therapies to treat the disease precludes the extrapolation of the efficacy of an agent in treating less complicated conditions such as amnesia to the treatment of this condition *per se*. In light of these reasons, the fact that one or two therapies known in the art may have shown efficacy in treating the cognitive symptoms seen with dementia, amnesia and Alzheimer's disease fails to provide a basis to assume that any pharmacologic therapy useful for treating any one of these conditions would necessarily

demonstrate the same (or substantially similar) level of efficacy in treating any one or more of the other conditions claimed. Accordingly, in view of the many distinct differences between these three claimed cognitive disorders, the required election of species is respectfully maintained.

Applicant is also reminded that, with regard to the present election of species requirement, the species elections were set forth for examination purposes and, should the elected species be found allowable, search and examination will be expanded to other claimed species of (a) cognitive disorder, (b) clavulanic acid compound and/or (c) P-glycoprotein efflux pump inhibitor.

Therefore, for the reasons above and those made of record at pages 2-10 of the previous Office Action dated September 22, 2006 and pages 2-6 of the previous Office Action dated April 23, 2007, the requirement remains proper and is hereby made **FINAL**.

Claims 1, 4, 7-10 and 12-17 are **withdrawn** pursuant to 37 C.F.R. 1.142(b) as being drawn to non-elected subject matter.

The claims corresponding to the elected subject matter are claims 2-3, 5-6 and 11 and such claims are herein acted on the merits.

Clarification of Continuation Status

Applicant's declaration filed July 15, 2003 stated that the instant application was a continuation of U.S. Patent Application No. 09/640,362, whereas page 1 of the specification filed July 15, 2003 stated that the instant application was a continuation of U.S. Patent Application No. 09/640,363. A Preliminary Amendment filed February 20, 2007 erroneously amended page 1 of the specification following the title from claiming priority to U.S. Patent Application No. 09/640,362 to now claim priority to U.S. Patent Application No. 09/640,363. Please note that this was clearly in error, since p.1 of the specification as filed July 15, 2003 already claimed priority to 09/640,363. Amendments filed on July 23, 2007 and

October 31, 2007 each amended page 1 of the specification from claiming priority to U.S. Patent Application No. 09/640,363 to now claim priority to U.S. Patent Application No. 09/640,362.

Applicant is requested to clarify the continuing status of the instant application. It is unclear whether Applicant intends to claim priority under 35 U.S.C. 120 to U.S. Patent Application No. 09/640,362 or U.S. Patent Application No. 09/640,363, each filed August 16, 2000. For the purposes of examination, Applicant's priority claim will be considered based upon the most recent amendment to the specification filed February 21, 2008, stating that the instant application is a continuation of U.S. Patent Application No. 09/640,362.

Please note that the instant discrepancy will have no effect on examination for the purposes of identifying prior art, since both the '362 and '363 applications were both filed on August 16, 2000. However, for clarity of the record, Applicant is requested to provide a clear statement on the record as to which application the instant application claims priority.

Double Patenting

Obviousness-Type Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 2-3, 5-6 and 11 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-4 of U.S. Patent No. 6,426,342 in view of Pfister et al. (U.S. Patent No. 5,889,007; 1999).

An obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but an examined application claim is not patentably distinct from the reference claims because the examined claims are either anticipated by, or would have been obvious over, the reference claims.

Although the conflicting claims are not identical, the claims of the instant patent application and those of the copending patent application or patents are not considered patentably distinct from each other because the patented claims render the present claims obvious.

The patented claims clearly provide for a method of treating a patient suffering from or susceptible to a condition known to result in loss of neuronal cells or less of neuronal cell function by reducing neuronal cell lose or function resulting from such conditions comprising the step of administration to said patient a neuroprotective amount of a bacterial beta-lactamase inhibitor (patented claim 1), such as clavulanic acid (patented claim 3). The patented claims further provide for a method for preventing neuron damage or the progression of neuronal damage in a patient suffering from or susceptible to disease states causing such neuronal damage comprising the step of administering to the patient a neuroprotective amount of a bacterial beta-lactamase inhibitor (patented claim 2), such as clavulanic acid (patented claim 4).

Though the patented claims do not specifically recite the treatment of dementia as the condition known to result in loss of neuronal cells or loss of neuronal cell function or the disease state that causes neuronal damage (patented claims 1-4), Applicant is directed to col.3, l.31-40, which defines the conditions known to result in loss of neuronal cells or loss of neuronal cell function to be, *inter alia*, various forms of dementia (including multi-infarct dementia, vascular dementia and neurodegenerative dementia). Though dementia is defined in the context of a condition known to result in the loss of neuronal cells or loss of neuronal cell function and not explicitly a condition that causes neuronal damage, the fact that the disclosed types of dementia are taught as being conditions that result in loss of neuronal

cells or neuronal cell function is understood to also be a disease state that causes neuronal damage as in patented claims 2 or 4 (since loss of neuronal cell function is considered to be "damage" to the neuronal cells). In the instant case, the disclosure of the patent application is being relied upon solely to define the meaning of the term "condition known to result in loss of neuronal cells or loss of neuronal cell function" or "disease state that causes neuronal damage" (patented claims 1-4), which is consistent with the MPEP at §804, which states, "The specification can be used as a dictionary to learn the meaning of a term used in the patent claim. *Toro Co. v. White Consol. Indus., Inc.,* 199 F.3d 1295, 1299, 53 USPQ2d 1065, 1067 (Fed. Cir. 1999)."

The patented claims fail to teach the concomitant use of the P-glycoprotein efflux pump inhibitor (2R)-anti-5-{3-[4-(10,11-difluoromethanodibenzosuber-5-yl)-piperazin-1-yl]-2-hydroxypropoxy}-quinoline (instant claims 5-6).

Pfister et al. teaches 10,11-methanodibenzosuberane derivative compounds, such as, *inter alia*, (2R)-anti-5-{3-[4-(10,11-difluoromethanodibenzosuber-5-yl)-piperazin-1-yl]-2-hydroxypropoxy}-quinoline (Example 6, compound (b) at col.20, l.17-20) for use in enhancing the bioavailability of a pharmaceutically active agent by administering to a mammal an effective amount of a compound of the disclosed formula [of which (2R)-anti-5-{3-[4-(10,11-difluoromethanodibenzosuber-5-yl)-piperazin-1-yl]-2-hydroxypropoxy}-quinoline is specifically exemplified in Example 6, compound (b) at col.20, l.17-20] sufficient to increase permeation of the active agent through the blood-brain barrier (col.3, l.23-29). Pfister et al. teaches that chemosensitizing agents (such as those disclosed therein) interact with the P-glycoprotein drug efflux pump by blocking the pump, which results in enhanced permeation of active agents through the blood brain barrier (col.1, l. 53-61).

One of ordinary skill in the art at the time of the invention would have found it *prima facie* obvious to use and administer the compound (2R)-anti-5-{3-[4-(10,11-difluoromethanodibenzosuber-5-yl)-piperazin-1-yl]-2-hydroxypropoxy}-quinoline in combination with the clavulanic acid of the patented

claims because such a compound was known to enhance the bioavailability of pharmaceutically active agents by increasing permeation of the agent through the blood-brain barrier, as evidenced by Pfister et al. Such a person would have been motivated to do so in order to increase plasma concentrations of the active agent to effective levels and also to enhance penetration of the clavulanic acid through the blood brain barrier into the brain to contact (and thereby treat) damaged neuronal cells.

Accordingly, rejection of claims 2-3, 5-6 and 11 is proper over claims 1-4 of U.S. Patent No. 6,426,342 as claiming obvious and unpatentable variants thereof.

Claims 2-3, 5-6 and 11 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-2 and 5-6 of U.S. Patent No. 6,610,681 in view of Pfister et al. (U.S. Patent No. 5,889,007; 1999).

An obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but an examined application claim is not patentably distinct from the reference claims because the examined claims are either anticipated by, or would have been obvious over, the reference claims.

Although the conflicting claims are not identical, the claims of the instant patent application and those of the copending patent application or patents are not considered patentably distinct from each other because the patented claims render the present claims obvious.

The patented claims clearly provide for a method of treating behavioral disorders in a patient in need of such treatment, wherein the behavioral disorder is, *inter alia*, aggressive disorder (patented claim 1) in a patient suffering from senile dementia (patented claim 2), comprising administering a clavulanic acid in an amount effective to modify patient behavior. The patented claims further provide for the additional administration of an effective amount of a P-glycoprotein efflux pump inhibitor compound as an additional step (patented claim 5) or in combination with the clavulanic acid (patented claim 6).

The patented claims fail to teach the concomitant use of the P-glycoprotein efflux pump inhibitor (2R)-anti-5-{3-[4-(10,11-difluoromethanodibenzosuber-5-yl)-piperazin-1-yl]-2-hydroxypropoxy}-quinoline (instant claims 5-6).

Pfister et al. teaches 10,11-methanodibenzosuberane derivative compounds, such as, *inter alia*, (2R)-anti-5-{3-[4-(10,11-difluoromethanodibenzosuber-5-yl)-piperazin-1-yl]-2-hydroxypropoxy}-quinoline (Example 6, compound (b) at col.20, l.17-20) for use in enhancing the bioavailability of a pharmaceutically active agent by administering to a mammal an effective amount of a compound of the disclosed formula [of which (2R)-anti-5-{3-[4-(10,11-difluoromethanodibenzosuber-5-yl)-piperazin-1-yl]-2-hydroxypropoxy}-quinoline is specifically exemplified in Example 6, compound (b) at col.20, l.17-20] sufficient to increase permeation of the active agent through the blood-brain barrier (col.3, l.23-29). Pfister et al. teaches that chemosensitizing agents (such as those disclosed therein) interact with the P-glycoprotein drug efflux pump by blocking the pump, which results in enhanced permeation of active agents through the blood brain barrier (col.1, l. 53-61).

One of ordinary skill in the art at the time of the invention would have found it *prima facie* obvious to use and administer the chemosensitizing compound (2R)-anti-5-{3-[4-(10,11-difluoromethanodibenzosuber-5-yl)-piperazin-1-yl]-2-hydroxypropoxy}-quinoline as the P-glycoprotein efflux pump inhibitor in combination with the clavulanic acid of the patented claims because such a compound was known to enhance the bioavailability of pharmaceutically active agents by increasing permeation of the agent through the blood-brain barrier, as evidenced by Pfister et al. Such a person would have been motivated to do so in order to increase plasma concentrations of the active agent to effective levels and also to enhance penetration of the clavulanic acid through the blood brain barrier into the brain to ameliorate the behavioral disorders originating from brain dysfunction.

Accordingly, rejection of claims 2-3, 5-6 and 11 is proper over claims 1-2 and 5-6 of U.S. Patent No. 6,610,681 as claiming obvious and unpatentable variants thereof.

Claims 2-3, 5-6 and 11 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 3, 6-7, 9-10, 14-15, 18, 27-28, 30 and 33-38 of U.S. Patent No. 6,627,625 in view of Pfister et al. (U.S. Patent No. 5,889,007; 1999).

An obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but an examined application claim is not patentably distinct from the reference claims because the examined claims are either anticipated by, or would have been obvious over, the reference claims.

Although the conflicting claims are not identical, the claims of the instant patent application and those of the copending patent application or patents are not considered patentably distinct from each other because the patented claims render the present claims obvious.

The patented claims clearly provide for a method of treating behavioral disorders in a patient in need of such treatment, wherein the behavioral disorder is, *inter alia*, aggressive disorder (patented claim 1) in a patient suffering from senile dementia (patented claim 3), comprising administering an effective amount of a beta-lactam compound, such as a beta-lactamase inhibitor (patented claim 6) or clavam compound (patented claim 7). The patented claims further provide for the additional administration of an effective amount of a P-glycoprotein efflux pump inhibitor compound as an additional step (patented claim 9) or in combination with the clavulanic acid (patented claim 10). The patented claims also provide for a method of treating behavioral disorders (such as, *inter alia*, aggressive disorder in a patient suffering from senile dementia; see patented claims 1-2) in a human comprising the step of administering a beta-lactam compound effective to inhibit the activity of a neurogenic peptidase (patented claims 14-15, 27-28 and 30 specify that the peptidase is one other than NAALADase) (patented claims 14-15, 18, 27-28 and 30). Further, the patented claims specify that the beta-lactam compound is administered in an effective amount of about 1 to about 150 mg per dose and may also be administered by mouth, in a prolonged release dosage form, in a lozenge dosage form, transdermally or parenterally (patented claims 33-38).

Though the patented claims do not specifically recite the use of clavulanic acid as the beta-lactam compound for administration, Applicant is directed to col.10, l.13-30, which defines the beta-lactam compounds that may be used in the context of the disclosed invention to be, *inter alia*, clavams or clavulanic acid. In the instant case, the disclosure of the patent application is being relied upon solely to define the meaning of the term "beta-lactam compound", which is consistent with the MPEP at §804, which states, "The specification can be used as a dictionary to learn the meaning of a term used in the patent claim. *Toro Co. v. White Consol. Indus., Inc.,* 199 F.3d 1295, 1299, 53 USPQ2d 1065, 1067 (Fed. Cir. 1999)."

The patented claims fail to teach the concomitant use of the P-glycoprotein efflux pump inhibitor (2R)-anti-5-{3-[4-(10,11-difluoromethanodibenzosuber-5-yl)-piperazin-1-yl]-2-hydroxypropoxy}-quinoline (instant claims 5-6).

Pfister et al. teaches 10,11-methanodibenzosuberane derivative compounds, such as, *inter alia*, (2R)-anti-5-{3-[4-(10,11-difluoromethanodibenzosuber-5-yl)-piperazin-1-yl]-2-hydroxypropoxy}-quinoline (Example 6, compound (b) at col.20, l.17-20) for use in enhancing the bioavailability of a pharmaceutically active agent by administering to a mammal an effective amount of a compound of the disclosed formula [of which (2R)-anti-5-{3-[4-(10,11-difluoromethanodibenzosuber-5-yl)-piperazin-1-yl]-2-hydroxypropoxy}-quinoline is specifically exemplified in Example 6, compound (b) at col.20, l.17-20] sufficient to increase permeation of the active agent through the blood-brain barrier (col.3, l.23-29). Pfister et al. teaches that chemosensitizing agents (such as those disclosed therein) interact with the P-glycoprotein drug efflux pump by blocking the pump, which results in enhanced permeation of active agents through the blood brain barrier (col.1, l. 53-61).

One of ordinary skill in the art at the time of the invention would have found it *prima facie* obvious to use and administer the chemosensitizing compound (2R)-anti-5-{3-[4-(10,11-difluoromethanodibenzosuber-5-yl)-piperazin-1-yl]-2-hydroxypropoxy}-quinoline as the P-glycoprotein

efflux pump inhibitor in combination with the clavulanic acid of the patented claims because such a compound was known to enhance the bioavailability of pharmaceutically active agents by increasing permeation of the agent through the blood-brain barrier, as evidenced by Pfister et al. Such a person would have been motivated to do so in order to increase plasma concentrations of the active agent to effective levels and also to enhance penetration of the clavulanic acid through the blood brain barrier into the brain to ameliorate behavioral disorders originating from brain dysfunction.

Accordingly, rejection of claims 2-3, 5-6 and 11 is proper over claims 1, 3, 6-7, 9-10, 14-15, 18, 27-28, 30 and 33-38 of U.S. Patent No. 6,627,625 as claiming obvious and unpatentable variants thereof.

Conclusion

The prior art made of record and not relied upon is considered pertinent to Applicant's disclosure. Please reference the publication to Drummond et al. ("Synthesis of a Cognition Enhancing Beta-Lactam Fused Gamma-Lactam", *Tetrahedron Letters*, 28(44); 1987:5245-5248) and U.S. Patent No. 4,110,165 to Cole et al. ("Process for the Production of Clavulanic Acid").

Rejection of claims 2-3, 5-6 and 11 is proper.

Claims 1, 4, 7-10 and 12-17 are **withdrawn** from consideration pursuant to 37 C.F.R. 1.142(b).

No claims of the present application are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Leslie A. Royds whose telephone number is (571)-272-6096. The examiner can normally be reached on Monday-Friday (9:00 AM-5:30 PM).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin H. Marschel can be reached on (571)-272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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